Cell Product Reporting Workshop

Review of FDA Reporting Requirements for Cell Products

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Definitions: Adverse Reaction Adverse Experience

- *Adverse reaction* (§1271.3(y)) : A noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response
- *Adverse experience* (§600.80(a)): Any adverse event associated with use of a biological product, whether or not considered product related, including:
  - Event occurring in course of use in professional practice
  - Event occurring from overdose, abuse, or withdrawal
  - Failure of expected pharmacological action

Definitions: Adverse experience (IND safety reports §312.32(a))

- *Serious adverse drug experience*: Any adverse drug experience that results in
  - Death
  - Immediate risk of death from reaction
  - Hospitalization or prolongation of hospitalization
  - Disability/incapacity
- *Unexpected adverse drug experience*:
  - Any adverse drug experience, the specificity or severity of which is not consistent with current investigator brochure or general investigational plan
  - Not previously observed

Adverse Reaction Reporting
21 CFR 1271.350(a) (361 HCT/P)

All HCT/P adverse reactions involving a communicable disease related to a product made available for distribution:

- Must be investigated by the manufacturer
- Must be reported if the adverse reaction:
  - Is fatal or life-threatening;
  - Results in permanent impairment of function or permanent damage to body structure; or
  - Necessitates medical or surgical intervention
- Report using Form FDA-3500A within 15 days

Reporting of adverse drug experiences
21 CFR 312.32-312.33 (351 Pre-licensure)

- **IND safety reports**
  - Required for any AE associated with use of the drug that is both serious and unexpected
  - Who reports: IND sponsor
  - Within 15 days of receipt of initial information
- **Annual reports**
  - Summary showing most frequent and serious Adverse Experiences
  - Summary of all IND safety reports for past year

Postmarketing Reporting of Adverse Experiences
21 CFR 600.80 (351 Post-licensure)

- Reporting required for each adverse experience that is both serious and unexpected
  - Who reports: licensed manufacturer
  - Timeframe: Within 15 days of receipt of initial information
  - Format: FDA Form 3500A (Medwatch)
- Periodic reporting for adverse experiences that are not both serious & unexpected
  - Quarterly reports for 3 years, then annual reports thereafter

Definitions: Deviation

- *HCT/P deviation* (21 CFR 1271.3(dd) :
  - A deviation from applicable regulations in this part or from applicable standards or established specifications that relate to prevention of communicable disease transmission or HCT/P contamination; or
  - An unexpected or unforeseeable event that may relate to the transmission/potential transmission of a communicable disease or may lead to HCT/P contamination
- *Biological product deviation* (§600.14)
  - Event a/w manufacturing, holding, or distribution of licensed product if it represents a deviation from CGMP, applicable regulations and standards, or specifications that may affect safety, purity, or potency of the product

Deviation Reporting
21 CFR 1271.350(b) (361 HCT/P)

All HCT/P deviations related to a distributed product:

- Must be investigated by the manufacturer
- Must be reported if:
  - Deviation occurred in your facility or in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement
  - Deviation related to "Core CGTPs"
- Form FDA 3486 Biological Product Deviation Report submitted within 45 days

Biological Product Deviations (351 Pre-licensure)

- No specific IND deviation reporting requirements
  - CGMP applicable to Phase 2 & 3 investigational products
    - "Any unexplained discrepancy… or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed…A written record of the investigation shall be made and shall include the conclusions and followup." (§ 211.192)
  - CBER Draft Guidance, 8/01: Report deviations that occur in the manufacture of unlicensed material used as part of an IND application through the IND mechanism
- Investigation should be performed and documented

Biological Product Deviations
21 CFR 600.14 (351 Post-licensure)

- Report “any event associated with manufacturing (including testing, processing, packing, labeling, or storage) or with holding or distribution of a licensed biological product, in which the safety, purity, or potency of a distributed product may be affected”
  - Who reports: Licensed manufacturer
  - When: Within 45 days from discovery, to OCBQ
  - Format: Form FDA 3486, Biological Product Deviation Report

	361	351 Pre-licensure	351 Post-licensure
Adverse reaction	CGTP § 1271.350(a)	Not applicable	Not applicable
Adverse experiences	Not applicable	IND Safety Reports & Annual Reports § 312.32-312.33	Biological Product Post Marketing Reports § 600.80
Deviations	CGTP § 1271.350(b)	IND procedures	BPDRs § 600.14

Recent experience – Cell product reporting for 2005

HCT/P Deviation reports

- Approximately 30 reports for HPCs
- Many involve (potentially) contaminated HPCs
- Many non-reportable
  - 351 products
  - Not related to core GTP

HCT/P Adverse reaction reports

- Approximately 60 reports for cell products
- Many non-reportable
  - Not infection-related
  - Opportunistic infection in recipient
  - No reaction